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REMARKS

Claims 19-24 have been added and claims 1, 2, 5 and 6 have been amended.
Accordingly, claims 1-24 are in the application.

Attached hereto is a marked-up version of the changes made to the claims by the above amendments. In the attached marked-up version of the claim amendments, additions are underlined and deletions are bracketed.

Rejection Under 35 U.S.C. 112

Claims 1, 2, 5, 6 and 8 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner has taken the position that the term “substantially pure” is “unnecessary and undesirable when a structural formula is given.” Applicants respectfully disagree. The claims distinguish over the prior art based on substantial purity. The expression “substantially pure” is not indefinite, and is defined in the specification. More specifically, at page 6, lines 5-7, it is stated that “By substantially pure is meant a compound which . . . is not shown to have any or any significant amount of contaminants detectable thereby.”

The essential inquiry pertaining to the definiteness requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed in light of the disclosure, the teachings of the prior art and the interpretation that would be given by one possessing an ordinary level of skill in the art. It is respectfully submitted that when the definition set forth in the specification is considered, and when the proper standard is applied, those having ordinary skill in the art would be able to ascertain the meaning of the claims with a reasonable degree of certainty.

As requested, we have deleted the word “general” from the claims.

The Examiner has also indicated that the meaning of the expression “a simple heteroatom-containing group” is indefinite. Applicants respectfully disagree. The meaning of the expression is adequately described, and numerous examples are provided at page 8, lines 3-17 of the specification. There are 61 U.S. Patents that have issued since 1996 that include the word “hetero-atom” in the claims. There are another 1,682 patents that have issued since

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1996 with claims containing the expression "heteroatom." Thus, there is ample evidence that those having ordinary skill in the art would understand, without an unreasonable degree of certainty, the meaning of the expression "a simple heteroatom-containing group."

As requested by the Examiner, the word "compounds" in claims 2, 5 and 6 have been replaced with the words "a compound."

The Examiner has also taken the position that claim 8 is indefinite because "claim 1 does not permit 'Q' to be a group of the formula X(Y) N-, but there is no indication that either 'X' or 'Y' can be an amidino group." Applicants respectfully disagree with this statement because, at page 8, lines 4-5, it is stated that "Examples of acyclic groups include the amidino group (to form, with the nitrogen atom to which X and Y are attached, a guanidino group)." Thus, it is expressly contemplated that claim 1 can encompass compounds wherein "Q represents . . . a group of formula XYN-, " where X and Y are acyclic groups which "form, with the nitrogen atom to which X and Y are attached, a guanidino group." The claims allow Q to, and the specification explains how Q can, represent a guanidino group. Therefore, the claims meet the requirements of 35 U.S.C. §112, second paragraph.

In view of the above amendments and remarks, it respectfully submitted that the claims comply with the definiteness requirements of 35 U.S.C. §112, second paragraph.

Prior Art Rejections

Claims 1, 2, 5, 6 and 8 have been rejected under 35 U.S.C. §102(b) as being anticipated by Cherksey (WO 93/12777), claim 1 has been rejected under 35 U.S.C. §102(b) as being anticipate by Cherksey U.S. Patent No. 5,424,947 (having a disclosure which is apparently identical to the disclosure of WO 93/12777), and claim 1 has been rejected under 35 U.S.C. §102(b) as being anticipated by Cherksey U.S. Patent No. 5,424,202.

The claims distinguish over the teachings of the applied Cherksey references, none of which teach or suggest the claimed compound in substantially pure form. Although the Cherksey references disclose the formulae of compounds that overlap with formula (I) of claim 1, the Cherksey references do not provide an enabling disclosure of those compounds such that they would be "substantially pure." As explained at pages 1 and 2 of the Applicants' specification, the prior art compositions are not prepared in substantially pure form. To the

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contrary, it is believed that the disclosed substances contain contaminants, and specifically do not meet the substantial purity requirement set forth at page 6, lines 5-11 for Applicants' specification.

While the Cherksey references state generally that the polyamine compounds "can be synthesized using well-known and commercially available starting materials and synthetic schemes well-known in the art," or that they "may be obtained from commercial sources," the specific syntheses disclosed in the Cherksey references are not suitable for preparing substantially pure compounds according to the claimed invention. Specifically, the Cherksey references disclose the synthesis of compound (B) and compounds (BB and BB'), but do not disclose synthesis of these compounds in substantially pure form as required by the claims.

In the synthesis of compound (B), L-Arg-ethyl ester was placed into a sodium hydroxide solution. This presents risks of ester hydrolysis and racemisation. Also during the synthesis of compound (B) triamine is added (pH 14), which again presents the risks of ester hydrolysis and racemisation. The polyamide used by Cherksey has three reactive amines, any of which could displace the ester, and thus a mixture of compounds would result. Further, the arginine ethyl ester has an unprotected amine. This will lead to polymerization of the arginine ethyl ester monomer and other side reactions. The resulting mixture (refer to as compound (B) by the Cherksey references) was not purified, but was instead used after neutralization, which results in high salt concentrations. Accordingly, the compound (B) taught by the Cherksey references is not substantially pure.

Compounds (BB) and (BB') were also made in an inappropriate manner such that a large mixture of compounds would result. In order to demonstrate this, compounds (B) and (BB') were prepared by the inventors following the synthetic methodology taught in WO 93/12777 and WO 91/00853. No activity was observed in the cultures, and they were found to be toxic, and therefore not substantially pure. Compound (B) as prepared in the WO 93/12777 killed rats. However, when the compound with the same formula was prepared in substantially pure form in accordance with the invention, the compound did not exhibit toxicity and was found to be neuroprotective in the inventors' 4VO model of cerebral ischaemia.

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Thus, compounds (B) and (BB') made according to WO 93/12777 or WO 91/00853 were not substantially pure, and were not the predominant chemical entity in the synthesis reaction product.

Because the Cherksey references do not teach preparing a pure or substantially pure preparation of the claimed compounds, there is not a specific enabling anticipation of the substantially pure compounds claimed in the present application. Moreover, the Cherksey references fail to teach the criticality of ensuring a substantially pure compound for an effective neuroprotective product. By contrast, the present application teaches that the compounds must be prepared in substantially pure form in order to achieve surprisingly neuroprotective, non-toxic medicinal results. Further, the present application discloses clearly how a substantially pure preparation can be made, in contrast to the disclosures in the Cherksey references, which teach synthesis of impure, toxic products.

While it is evident that the Cherksey et al. references do not expressly teach preparation of the claimed compounds in substantially pure form, Applicants submit with this response a declaration stating facts upon which a determination can be made that the compounds synthesized in accordance with the teachings of the Cherksey et al. references were not substantially pure as required.

In view of the absence of any express teaching by the Cherksey et al. references of substantially pure compounds having the formula (I) as set forth in the pending claims, and in view of the attached declaration that shows that the compounds prepared in accordance with the teachings of Cherksey et al. are not substantially pure, it is respectfully submitted that claims 1-18 are allowable over the applied prior art references.

New Claims

Claims 19-24 have been added to further distinguish over the prior art, which does not teach or suggest non-toxic compositions containing the compounds of formula (I), compositions containing less than 1% contaminants, or compositions "consisting essentially of a compound having formula (I)." Accordingly, it is respectfully submitted that these claims are also allowable over the applied prior art references.

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CONCLUSION

In view of the above amendments and remarks, it is submitted that the application is in condition for allowance and notice of the same is requested.

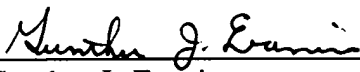
Respectfully submitted,

LARS E. SUNDSTROM ET AL.

By: Price, Heneveld, Cooper,
DeWitt & Litton

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Date

GJE/daw



Gunther J. Evanina
Registration No. 35 502
695 Kenmoor S.E.
P.O. Box 2567
Grand Rapids, Michigan 49501
(616) 949-9610

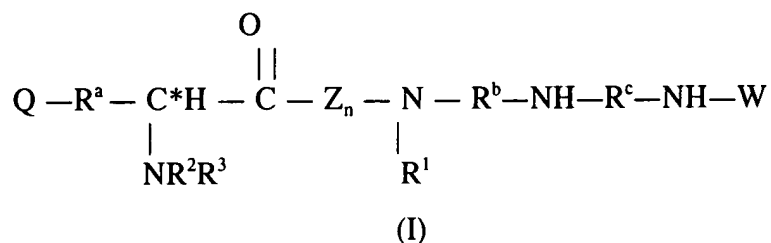
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 2, 5 and 6 have been amended as follows:

1. (Amended) A substantially pure compound having the [general] formula (I)



wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl groups, or simple hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

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R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents a, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents a, defined below;

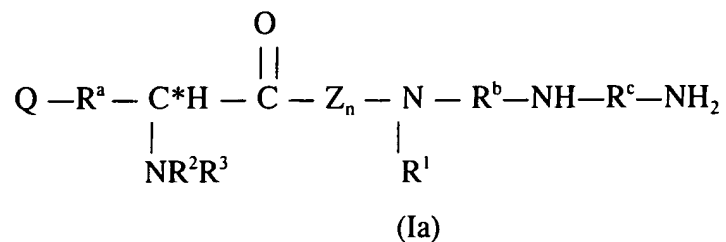
W represents a hydrogen atom or an alkyl or aryl group; and

substituents a are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is alkyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof.

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2. (Amended) [Compounds] A compound according to Claim 1, having the formula (Ia):



wherein Q, R^a, R^b, R^c, R², R³, Z, n, and R¹ are as in Claim 1.

5. (Amended) A [Non-toxic compounds] non-toxic compound of formula (I) as defined in Claim 1.

6. (Amended) A [Non-toxic compounds] non-toxic compound of formula (Ia) as defined in Claim 2.